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Childhood risk factors and carotid atherosclerotic plaque in adulthood: The Cardiovascular Risk in Young Finns Study

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Manuscript contains three tables and two figures. Figure 1 and 2 titles and legends are at the end of the article file.

Keywords

Atherosclerosis; Carotid atherosclerotic plaque; Childhood cardiovascular risk factors; Cardiovascular risk factor cut-offs; Area under the curve – childhood risk factor long-term burden

Abstract

Background and aims

Carotid plaque is a specific sign of atherosclerosis and adults with carotid plaque are at increased risk for cardiovascular outcomes. Atherosclerosis has roots in childhood and pediatric guidelines provide cut-off values for cardiovascular risk factors. However, it is unknown whether these cut-offs predict adulthood advanced atherosclerosis.

Methods

The Cardiovascular Risk in Young Finns Study is follow-up of children begun in 1980 when 2653 participants with data for present analyses were aged 3-18 years. In 2001 and 2007 follow-ups, in addition to adulthood cardiovascular risk factors, carotid ultrasound data was collected. Long-term burden as the area under the curve was evaluated for childhood (6-18 years) risk factors. To study the associations of guideline-based cut-offs with carotid plaque, both childhood and adult risk factors were classified according to clinical practice guidelines.

Results

Carotid plaque, defined as focal structure of arterial wall protruding into lumen >50% compared to adjacent intima-media thickness, was present in 88 (3.3%) participants. Relative risk for carotid plaque, when adjusted for age and sex, was 3.03 (95%CI, 1.76-5.21) for childhood dyslipidemia, 1.51 (95%CI, 0.99-2.32) for childhood elevated systolic blood pressure, and 1.93 (95%CI, 1.26-2.94) for childhood smoking. Childhood dyslipidemia and smoking remained independent predictors of carotid plaque in models additionally adjusted for adult risk factors and family history of coronary heart disease. Carotid plaque was present <1% of adults with no childhood risk factors.

Conclusions

Findings reinforce childhood prevention efforts and demonstrate the utility of guideline-based cut-offs in identifying children at increased risk for adulthood atherosclerosis.

Introduction

Cardiovascular diseases with atherosclerotic etiology, are the leading cause of mortality worldwide.[1] Although the clinical complications of atherosclerosis typically present in middle to older age, the disease process has a long silent stage that commences in early life.[2–4] Longitudinal studies have shown that the association between childhood cardiovascular risk factors and adult preclinical atherosclerosis is not completely reversed by the improvement of risk factors from childhood to adulthood.[5,6] Recognizing that atherosclerosis is a lifelong disease, best clinical practice guidelines have been issued by leading authorities for application in children and adolescents.[7–9] These guidelines are aimed at the primordial and primary prevention of cardiovascular risk factors and behaviors shown to accelerate atherosclerosis development.

The association of pediatric cut-offs recommended in guidelines has been shown for child low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol with adult high carotid artery intima-media thickness (cIMT), and child blood pressure with adult increased arterial stiffness.[10,11] While cIMT and arterial stiffness are considered early markers of atherosclerosis, these phenotypes may not be entirely specific for atherosclerosis, as they can also reflect medial hypertrophy.[12] Instead, distinct carotid atherosclerotic plaques that can be detected using non-invasive ultrasound are considered a more specific indicator of ongoing atherosclerosis,[12] and compared to cIMT are more strongly associated with clinical cardiovascular outcomes.[13] However, no previous studies have examined the utility of guideline-based cut-offs for childhood risk factor levels in predicting manifest atherosclerosis, such as carotid plaque, in adulthood. Moreover, no data have yet determined the independent effect of the long-term exposure to early life risk factors on carotid plaque.

Therefore, using data from a prospective cohort of children, we aimed to examine the association of childhood risk factors long-term burden, classified according to clinical practice guidelines, with carotid plaque almost three decades later. In addition, by using risk factor data both in childhood and adulthood, we tested the 'childhood origins' hypothesis by examining whether childhood exposure to risk factor levels exerts an effect on adult atherosclerosis that is independent of adult risk factor exposure.

Patients and methods

Study population

The Cardiovascular Risk in Young Finns Study is an ongoing multicenter follow-up study that was conducted in five Finnish cities (Helsinki, Kuopio, Oulu, Tampere, and Turku) and their rural surroundings. In 1980, 4320 children aged 3, 6, 9, 12, 15, and 18 years were randomly chosen from the national population register of these areas and invited to participate in the study. Of those invited, 3596 children participated in the first cross-sectional survey.[14] Since then, follow-up studies have been conducted in 1983, 1986, 1989, 1992, 2001, 2007, and 2011. The entire cohort was invited to participate in follow-up studies in 1983, 1986, 2001, 2007, and 2011 when 2991, 2799, 2620, 2243, and 2115 subjects participated, respectively. In 1989 and 1992, physical examination and blood tests were gathered from a part of the cohort. In addition, during these two follow-ups background information questionnaire was gathered from the entire cohort.[15] Carotid ultrasound studies and adulthood cardiovascular risk factors were collected in 2001 and 2007 follow-ups when participants were aged 24-45 years. Altogether, carotid ultrasound was performed to 2653 subjects in 2001 or 2007, comprising the study cohort for this analysis. Flowchart for the Cardiovascular Risk in Young Finns Study is provided in the Supplemental material (Supplemental Table 1). The study was approved by

local ethics committees and was performed according to the Declaration of Helsinki. Written informed consent was obtained from all participants or their parents.

Cardiovascular risk factors

In 1980, systolic blood pressure was measured with an ultrasound scanning device (Arteriosonde 1020, Roche) in participants aged 3 years. For all other participants, blood pressure was measured with a standard mercury sphygmomanometer in 1980 and 1983, and from 1986 onward using a random zero sphygmomanometer. At each visit, blood pressure was measured three times and the average of these three measurements was used in the analyses. Diastolic blood pressure was determined from Korotkoff's fifth sound. Body mass index (BMI) was calculated from the measured weight in kilograms divided by the square of the measured height in meters. Standard methods were used to determine total cholesterol and triglyceride concentrations from fasting blood samples.[16] LDL-cholesterol was calculated indirectly using the Friedewald formula.[17] Due to high triglyceride levels, the Friedewald formula could not be applied to 57 adults. Based on elevated triglyceride levels, these individuals were classified as having dyslipidemia in adulthood. All childhood triglyceride levels were within acceptable limits to be included in the Friedewald formula for calculation of child LDL-cholesterol. HDL-cholesterol was analyzed after precipitation of very low-density lipoprotein and LDL-cholesterol with dextran sulfate 500000. Non-high-density lipoprotein (non-HDL) cholesterol was calculated as total cholesterol minus HDL-cholesterol. Family history of coronary heart disease (CHD) and smoking habits were collected using self-report questionnaires. Information on childhood smoking habits was collected from children aged 12-18 years. If a participant was aged less than 12 years in the first cross-sectional survey then information on childhood smoking habits was collected in the subsequent follow-ups.

Instead of using childhood risk factor measurements from a single time point, we leveraged repeatedly measured data from the longitudinal Cardiovascular Risk in Young Finns Study to describe long-term cumulative burden of childhood blood pressure, BMI, and serum lipids as detailed in the Supplemental material (Supplemental Methods and Supplemental Figure 1). In brief, we utilized several risk factor measurements from 1980 to 2011 to calculate the area under the curve (AUC) separately for each risk factor as a measure of risk factor long-term cumulative burden. First, subject-specific curves for the cardiovascular risk factors were estimated by mixed model regression splines.[18] Then, similar to the approach of Lai et al.[19] AUCs were evaluated for each risk factor. AUC variables were defined for the age period of 6-18 years indicating the risk factors long-term cumulative burden in childhood. For adulthood, risk factor measurements from a single time-point, either 2001 or 2007, was used. If carotid plaque was present or the only carotid ultrasound was performed in 2001, then risk factors from 2001 were used. Otherwise, risk factors from 2007 were used. This approach enabled comparison of childhood risk factors with the risk factors at the time of the carotid scan.

Cardiovascular risk factor classification

To study the associations of guideline-based cut-offs with carotid plaque, both childhood and adult risk factors were classified according to clinical practice guidelines.[8,9,20,21] Comparable cut-offs for childhood long-term cumulative burden was calculated and childhood risk factors were classified as abnormal if the long-term burden exceeded, or in case of HDL-cholesterol being below the cut-off. Elevated childhood blood pressure was defined as levels above 90th percentile or blood pressure ≥ 120/80 mmHg.[9] Elevated adult blood pressure was defined by grade 1 hypertension as blood pressure ≥ 140/90 mmHg or self-reported use of antihypertensive medicine.[21] Overweight in childhood was defined as per international age- and sex-specific BMI percentiles,[22] and adult overweight as BMI ≥ 25 kg/m^2. Abnormal childhood lipid levels

were defined using high cut-offs as total cholesterol ≥ 5.17 mmol/l (200 mg/dl), LDL-cholesterol ≥ 3.36 mmol/l (130 mg/dl), non-HDL-cholesterol ≥ 3.75 mmol/l (145 mg/dl), triglycerides ≥ 1.13 mmol/l (100 mg/dl) for ages ≤ 9 years, and ≥ 1.47 mmol/l (130 mg/dl) for ages 10-18 years, and low cut-off for HDL-cholesterol < 1.0 mmol/l (40 mg/dl).[8] Abnormal adulthood lipid levels were defined as total cholesterol > 5.0 mmol/l (190 mg/dl), LDL-cholesterol > 3.0 mmol/l (115 mg/dl), non-HDL-cholesterol > 3.8 mmol/l (145 mg/dl), triglycerides > 1.7 mmol/l (150 mg/dl), HDL-cholesterol < 1.0 mmol/l (40 mg/dl) in men, and < 1.2 mmol/l (48 mg/dl) in women.[20] Participants self-reporting current use of lipid-lowering medication were considered as having elevated total-, LDL-, and non-HDL-cholesterol. Dyslipidemia was defined as abnormality of any lipid value. Childhood smoking status was defined as positive for participants indicating they had ever smoked daily when aged 12-18 years and in adulthood if the participant indicated they were currently smoking daily. Family history of CHD was classified as positive if a participant indicated their father or mother had been diagnosed with CHD, experienced myocardial infarction or had percutaneous coronary intervention or coronary bypass surgery performed at < 55 years of age. In the 2007 questionnaire, mother's age was raised to < 65 years.

Carotid atherosclerotic plaque

Carotid ultrasound studies were performed on the left carotid artery including common carotid artery and carotid bifurcation using B-mode ultrasound (Sequoia 512; Acuson) with a 13.0 MHz linear-array transducer according to a standardized protocol.[5] Digitally stored images were scanned for the existence of carotid atherosclerotic plaques, defined as a focal structure of the arterial wall protruding into the lumen > 50% compared to the adjacent intima-media thickness.[23]

Statistical methods

Association between risk factors and carotid plaque

Poisson regression models with robust standard errors were used to calculate relative risks and 95% confidence intervals for carotid plaque according to risk factors. First, models for each childhood and adult risk factor were examined. Second, to evaluate the independent effect of childhood risk factors on the outcome, both childhood and adult risk factors were included into the same model. Third, multivariable models including all childhood and/or adult risk factors were created. All models were adjusted for sex and age. To test if sex modified the association between risk factors and carotid plaque, sex by risk factor interaction terms were examined. With the exception of adult overweight and BMI, no significant interaction was observed (p always >0.1). To evaluate potential collinearity between childhood and adult risk factors variance inflation factor values were examined.[24] All variance inflation factor values were < 1.7, indicating no prevailing collinearity. Systolic blood pressure was used in multivariable models due to low prevalence of elevated childhood diastolic blood pressure. To study the association of risk factor accumulation with carotid plaque an additive score for abnormal childhood and adult risk factors was calculated.

In sensitivity analyses, models were repeated after excluding participants with diabetes; adjusting for cIMT; and replacing family history of premature CHD with family history of CHD at any age. Because measures from the random zero sphygmomanometer may underestimate blood pressure levels, we repeated our analyses after adding 1.35 mmHg and 2.54 mmHg to random zero systolic and diastolic blood pressures, respectively.[25] Finally, regression models were repeated using Z-scores resulting in variables with mean 0 and SD 1. In all sensitivity analyses, associations remained essentially similar to the main results shown.

Statistical analyses were performed with SAS 9.4, and statistical significance was inferred at 2-sided $p<0.05$.

Results

Of the 2653 participants, carotid plaque was present in 88 (3.3%) individuals. All plaques were detected in carotid bifurcation. Mean length of follow up from first risk factor measurement was 25.9 (2.3) years. Prevalence of plaque was higher among males (4.7% vs. 2.2%, $p<0.001$) and those with plaque were, on average, older (38.2 [4.6] vs. 36.4 [5.6] years, $p<0.001$). Childhood and adult characteristics according to plaque status are displayed in Table 1.

Single risk factors and carotid plaque

Childhood risk factors that significantly associated with carotid plaque were elevated total cholesterol, LDL-cholesterol, non-HDL-cholesterol, dyslipidemia, and smoking. In addition, the effect of childhood elevated systolic blood pressure was of borderline significant (Table 2). Adult risk factors that significantly associated with carotid plaque were elevated total cholesterol, LDL-cholesterol, non-HDL-cholesterol, and dyslipidemia. The effect of adult smoking was of borderline significant. In addition, positive family history of CHD significantly associated with carotid plaque. After adjusting for adult risk factors, independent effects remained significant for childhood elevated total cholesterol, LDL-cholesterol, non-HDL-cholesterol, dyslipidemia, and smoking (indicated as residuals in Table 2). In analyses with Z-scores, results remained essentially similar except that the effects for childhood diastolic blood pressure and adult triglycerides were significant and adult HDL-cholesterol and BMI were inversely associated with carotid plaque (Supplemental Table 2).

In addition, we performed analyses to study the association of childhood smoking volume with the presence of adulthood carotid plaque. Childhood smoking volume was divided into four groups: never smoked; smoked 1 cigarette; smoked 2 to 50 cigarettes; smoked over 50 cigarettes during childhood. Across these four groups, carotid plaque prevalence increased from 1.9%, 2.3%, 4.0%, to 5.1%, respectively. Furthermore, we calculated relative risks for carotid plaque using the never smoked group as the reference category yielding relative risks of 1.14 (95% CI 0.42-3.09), 1.86 (95% CI 0.99-3.50), and 2.27 (95% CI 1.24-4.15), respectively [*p* for trend 0.005, (Supplemental Table 3)].

Multiple risk factors and carotid plaque

In the childhood multivariable risk model (Table 3, Model 1) dyslipidemia, smoking, and positive family history were significant predictors of carotid plaque. In an equivalent model but using adult risk factors (Table 3, Model 2), dyslipidemia and positive family history were significantly associated with carotid plaque. When the childhood model was additionally adjusted for adult risk factors (Table 3, Model 3), childhood dyslipidemia, smoking, and positive family history of CHD remained independent predictors of carotid plaque. Results were essentially similar with Z-scores (Supplemental Table 4).

Dyslipidemia, smoking, elevated systolic blood pressure, and positive family history of CHD were included into models for evaluating the effects of risk factor accumulation on carotid plaque prevalence. When the number of childhood risk factors increased, the proportion of participants with carotid plaque increased from 0 risk factors=1.0%, 1 risk factor=1.9%, 2 risk factors=5.9%, and 3 to 4 risk factors=8.7% (Figure 1). For adulthood risk factors, the proportion of participants with carotid plaque were 1.0%, 2.1%, 6.6%, and 5.2%, respectively (Supplemental Figure 2). Sex stratified figures are provided in the supplemental material

(Supplemental Figures 3 and 4). To evaluate the independent effect of childhood risk factor accumulation, we built a model that included both childhood and adult risk factors. The proportion of participants with carotid plaque increased as the number of childhood and adult risk factors increased (Figure 2).

Finally, the relative risk for carotid plaque was estimated according to the presence of 0 (reference), 1, 2, or 3 to 4 childhood risk factors. Relative risks were 1.9 (p=0.16), 5.7 (p<0.001), and 8.1 (p<0.001), respectively. The model was repeated adjusting for adult risk factors, yielding the relative risks of 1.6 (p=0.32), 3.9 (p=0.003), and 5.4 (p=0.001), respectively.

Discussion

We found that long-term exposure to cardiovascular risk factors in childhood predicted carotid atherosclerotic plaque three decades later. Irrespective of risk factor levels measured at the time carotid ultrasound was performed, childhood dyslipidemia and smoking were both associated with about a doubling of risk for having carotid plaque as an adult. Childhood elevated systolic blood pressure and a heightened continuous diastolic blood pressure levels were associated with a higher risk of having carotid plaque in adulthood, albeit the effect was of borderline significant for elevated systolic blood pressure. Our findings suggest a cumulative childhood risk factor burden on atherosclerosis that persists into adulthood.

Although child cardiovascular risk factors have been shown to predict markers of adult preclinical atherosclerosis such as cIMT, coronary calcification, and arterial elasticity independent of contemporary risk factor levels,[5,6,26] the independent association of childhood

risk factors with the development of carotid plaque has not previously been shown. Importantly, the effects observed for childhood dyslipidemia, diastolic blood pressure, and smoking were not attributable to tracking of these risk factors from childhood to adulthood, as the presence of childhood risk factors had a greater effect on mid-adulthood carotid plaque than contemporary risk factors. These data are consistent with the long stage of atherosclerosis and suggest that cumulative lipid levels, heightened blood pressure, and smoking in childhood may induce permanent changes in the vasculature that contribute to the development of manifest atherosclerosis later in life.

Childhood guidelines cut-offs associations have been demonstrated for child LDL- and HDL-cholesterol with adult high cIMT and child blood pressure with adult increased arterial stiffness.[10,11] Our results extend these findings to the presence of carotid plaque, a specific phenotype of active atherosclerosis,[12] that is more strongly influenced by modifiable risk factors, and has improved the predictive utility for cardiovascular diseases, especially to CHD, compared to cIMT.[13,27–32] To our knowledge, our study is the first to demonstrate the associations of childhood cardiovascular risk factors guideline-based cut-offs with adulthood advanced atherosclerosis.

Childhood diastolic blood pressure, as a continuous variable, was significantly associated with carotid plaque but the cut-off for systolic blood pressure showed only borderline significantly increased risk in this cohort. Because a random zero sphygmomanometer may underestimate blood pressure, we repeated our analyses after adding 1.35 mmHg and 2.54 mmHg to random zero systolic and diastolic blood pressures, respectively.[25] However, the results remained essentially similar. In addition, we repeated our analyses using the reference values from a recent blood pressure recommendation issued by the American Academy of Pediatrics.[33] The

cut-off values for elevated diastolic blood pressure in this treatment recommendation are lower than those recommended by the International Child Blood Pressure References Establishment Consortium.[9] However, the results remained essentially similar. This may suggest that the recommended cut-offs for childhood blood pressure, at least for diastolic blood pressure, are not optimal for predicting future atherosclerosis.

Childhood smoking is a well-known risk factor for atherosclerosis.[2,5,6,26] To our knowledge, the association between the amount of childhood smoking and adult atherosclerosis has not been previously studied. Instead, regular childhood smoking has been widely used as an exposure variable.[2,5,6,26] For this study, we performed additional analyses to study whether childhood smoking volume is associated with the presence of adult carotid plaque. When the childhood smoking volume was divided into four groups: never smoked; smoked 1 cigarette; smoked 2 to 50 cigarettes; smoked over 50 cigarettes, we observed plaque prevalence increase across these four groups from 1.9%, 2.3%, 4.0%, to 5.1%, respectively. In addition, relative risk for carotid plaque increased as the childhood smoking volume increased. Although further analyses are still needed with additional adjustment for other risk factor exposures, these findings highlight the importance of measures to reduce smoking in childhood.

Family history and genetics are well known predictors of atherosclerosis,[34] and our findings are in line with this previous knowledge. The effect of multiple childhood risk factors on atherosclerosis and markers of atherosclerosis has been observed.[2,5,26] Our data was consistent with these findings with the proportion of participants with carotid plaque increasing as the number of childhood risk factors increased. Notably, carotid plaque was present in less than 1% of participants with no childhood risk factors irrespective of their adult risk factors. These findings, to our knowledge, are the first to show the independent effect of childhood risk factor

accumulation on formation of carotid plaque in adulthood. Furthermore, findings suggest that a favorable childhood risk factor profile might be protective of atherosclerosis development, at least by mid-adulthood.

Of interest, we found neither childhood nor adult BMI to be associated with carotid plaque. Similar findings in adult studies have been observed.[28–31,35,36] Evidence on the role of child BMI on adult atherosclerosis is equivocal. In the present cohort, we have demonstrated that elevated BMI in childhood is associated with increased cIMT and decreased carotid distensibility in adulthood.[5,26] Furthermore, data from the International Childhood Cardiovascular Cohort Consortium showed that although elevated child BMI is a strong predictor of high adulthood cIMT, the effect tends to be attenuated with a non-obese BMI in adulthood.[37] Moreover in a subsample of the Cardiovascular Risk in Young Finns Study, we did not find an association between child BMI and adult coronary calcification.[6] Contrary to this, Tirosh et al. found that BMI at the end of adolescence was an independent predictor of angiography-confirmed coronary heart disease in men approximately 17 years later.[38] Similarly in the Muscatine study, childhood BMI was associated with coronary calcification in middle aged men.[39] The PDAY study found that BMI was associated with coronary artery atherosclerosis in men aged 15-34 years, however no association was seen for females.[3] Therefore, most available data indicate that elevated BMI in childhood predict the appearance of atherosclerotic phenotypes in adulthood and that there might be sex-difference. Findings from our cohort, when using specific adult atherosclerosis phenotypes as the outcomes, suggest that the effect of childhood adiposity on atherosclerosis may be weaker than previously assumed.

This study had limitations. Ultrasound scanning included only the left carotid artery and the protocol did not involve imaging of the internal carotid artery. However, plaque typically begins to form at the carotid bifurcation,[40] and previous studies among age-groups comparable to this study do not suggest a higher prevalence of carotid plaques.[29,35] Still, some misclassification might have occurred. Bias due to differential loss to follow-up is possible in prospective cohort studies. However, the Cardiovascular Risk in Young Finns Study has a high retention of participants relative to similar cohort studies and have shown that participants do not differ with non-participants except that participants are more likely to be females and of older age.[15,41] Strengths include the large, population-based cohort, who have been serially followed for risk factors from childhood to adulthood.

In summary, we showed that childhood guideline-based cut-offs applied to cumulative dyslipidemia, as well as smoking, and heightened diastolic blood pressure predicted adulthood carotid atherosclerotic plaque independent of concurrent risk factors. Our data highlights the importance of primordial prevention and demonstrates the utility of guideline-based cut-offs in identifying children with increased risk of developing advanced atherosclerosis later in life.

Conflict of interest

No potential conflict of interest was reported from any authors.

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Author contributions

JSK made substantial contributions to the conception and design of the study, analysis of the data, interpretation of the data, drafted the article, and revised it critically based on comments received from co-authors. VK co-supervised JSK, made substantial contributions to the conception and design of the study, analysis of the data, interpretation of the data, and writing the article. MJ made substantial contributions to the conception and design of the study, analysis of the data, interpretation of the data, and revised the article critically for important intellectual content. JSAV made substantial contributions to the conception and design of the study, interpretation of the data, and revised the article critically for important intellectual content. JN made substantial contributions to the conception and design of the study, analysis of the data, interpretation of the data, and revised the article critically for important intellectual content. MK, TL, NH-K, PT, and EJ made substantial contributions to the conception and design of the study and revised the article critically for important intellectual content. CGM co-supervised JSK, made substantial contributions to interpreting the data, and writing the article. OTR supervised the Cardiovascular Risk in Young Finns Study, co-supervised JSK, made substantial contributions to the conception and design of the study, analysis of the data, interpretation of the data, and writing the article.

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Figure 1. Proportion of participants with carotid plaque according to the number of childhood risk factors[a]

[a] One point was given for each risk factor classified as abnormal. Risk factors included were dyslipidemia, elevated systolic blood pressure, smoking, and family history of coronary heart disease. Carotid plaque (%) indicates the proportion of individuals with carotid plaque across different groups. Total n for 0, 1, 2, and 3 to 4 groups are 627, 1094, 711, and 219, respectively.

Figure 2. Proportion of participants with carotid plaque according to the number of childhood and adult risk factors[a]

[a] One point was given for each risk factor classified as abnormal. Risk factors included were dyslipidemia, elevated systolic blood pressure, and smoking. Carotid plaque (%) indicates the proportion of participants with carotid plaque in adulthood.

Childhood risk factors and carotid atherosclerotic plaque in adulthood: The Cardiovascular Risk in Young Finns Study

Highlights

- Cumulative child risk factors independently associate with adult carotid plaque.
- Less than 1% of adults with no risk factors in childhood had carotid plaque.
- Sustained cardiovascular health in childhood is needed to reduce future risk.

Table 1. Childhood and adult characteristics according to adult carotid plaque status. For childhood risk factors the means of the long-term burden are presented.[a]

	No plaque present		Plaque present	
	Statistic	**Percentage with abnormal levels**[b]	**Statistic**	**Percentage with abnormal levels**[b]
No. (%)	2565 (96.7)		88 (3.3)	
Age, mean (SD), year	36.4 (5.6)		38.2 (4.6)	
Sex, No. (%)				
Female	1410 (55.0)		31 (35.2)	
Male	1155 (45.0)		57 (64.8)	
Systolic blood pressure, mean (SD), mmHg[c]				
Childhood	111.1 (5.8)	23.0	112.9 (5.4)	35.2
Adult	120.2 (14.1)	13.8	123.9 (14.5)	20.5
Diastolic blood pressure, mean (SD), mmHg[d]				
Childhood	65.4 (4.9)	0.3	67.8 (4.0)	0
Adult	75.1 (11.4)	15.2	76.7 (11.6)	20.5
Lipids and lipoproteins, mean (SD), mmol/L[e]				
Total cholesterol[f]				
Childhood	5.2 (0.7)	49.9	5.5 (0.7)	70.5
Adult	5.1 (0.9)	47.6	5.6 (1.1)	69.3
LDL cholesterol[g]				
Childhood	3.4 (0.7)	48.5	3.8 (0.6)	76.1
Adult	3.1 (0.8)	52.0	3.7 (1.0)	75.6

HDL cholesterol[h]				
Childhood	1.5 (0.2)	0.9	1.4 (0.2)	1.1
Adult	1.3 (0.3)	23.8	1.2 (0.3)	26.4
Non-HDL cholesterol[i]				
Childhood	3.7 (0.7)	45.5	4.1 (0.7)	68.2
Adult	3.7 (0.9)	43.5	4.4 (1.1)	67.8
Triglycerides[j]				
Childhood	0.7 (0.2)	0.7	0.7 (0.2)	0
Adult	1.4 (0.9)	22.5	1.7 (1.5)	30.7
Dyslipidemia, No. (%)[k]				
Childhood	1455 (56.7)		71 (80.7)	
Adult	1784 (69.8)		78 (88.6)	
Body mass index, mean (SD), kg/m^2 [l]				
Childhood	18.4 (2.1)	8.1	18.2 (1.7)	6.8
Adult	25.9 (4.8)	51.9	25.6 (3.4)	54.6
Smoking, No. (%)				
Childhood	526 (20.5)		32 (36.4)	
Adult	525 (20.5)		26 (29.6)	
Family history of coronary heart disease, No. (%)				
	454 (17.7)		31 (35.2)	

[a] N=2565 in no plaque group and n=88 in plaque group unless stated otherwise.

[b] Risk factors were classified based on guideline-based cut-offs. Childhood risk factors were classified as abnormal if the long-term burden exceeded, or in case of HDL-cholesterol was below, the comparable cut-off.

[c] Two no plaque participants could not be classified due to missing height that is necessary for classifying childhood blood pressure. Adult n=2557 in no plaque group.

[d] Childhood n=2564 in no plaque group and adult n=2555 in no plaque group.

[e] To convert the values for cholesterol to mg/dL multiply by 38.67 and for triglycerides multiply by 88.57.

[f] Adult n=2555 in no plaque group.

[g] Adult n=2500 in no plaque group. Four participants with lipid lowering medication but no LDL cholesterol value are included to group with abnormal levels of adulthood LDL cholesterol. N=86 in adult plaque group.

[h] Adult n=2546 in no plaque group and n=87 in plaque group.

[i] Adult n=2546 in no plaque group and 3 participants with lipid lowering medication but no non-HDL cholesterol value are included to group with abnormal levels of adulthood non-HDL cholesterol. N=87 in adult plaque group.

[j] Adult n=2555 in no plaque group.

[k] Adult n=2555 in no plaque group.

[l] Adult n=2528 in no plaque group.

Table 2. Relative risks (RR) and 95% confidence intervals (CI) between childhood and adult risk factors and presence of adult carotid plaque[a]

	RR (95% CI)	*p* value
Elevated systolic blood pressure		
Childhood	1.51 (0.99-2.32)	0.06
Adult	1.23 (0.73-2.05)	0.44
Residual	1.49 (0.97-2.31)	0.07
Elevated diastolic blood pressure		
Childhood	nonestimable[b]	
Adult	1.09 (0.65-1.83)	0.74
Residual	nonestimable[b]	
Lipids and lipoproteins		
Elevated total cholesterol		
Childhood	2.32 (1.45-3.71)	<0.001
Adult	2.03 (1.30-3.18)	0.002
Residual	1.92 (1.16-3.16)	0.01
Elevated LDL cholesterol		
Childhood	3.20 (1.89-5.42)	<0.001
Adult	2.30 (1.42-3.74)	<0.001
Residual	2.80 (1.56-5.01)	<0.001
Low HDL cholesterol		
Childhood	1.02 (0.15-6.78)	0.98
Adult	1.17 (0.73-1.86)	0.51
Residual	0.92 (0.14-6.23)	0.93

Elevated non-HDL cholesterol		
Childhood	2.42 (1.54-3.81)	<0.001
Adult	2.15 (1.36-3.40)	0.001
Residual	1.96 (1.19-3.24)	0.009
Elevated triglycerides		
Childhood	nonestimable[b]	
Adult	1.21 (0.77-1.91)	0.41
Residual	nonestimable[b]	
Dyslipidemia		
Childhood	3.03 (1.76-5.21)	<0.001
Adult	2.78 (1.45-5.33)	0.002
Residual	2.50 (1.42-4.42)	0.002
Overweight		
Childhood	0.93 (0.41-2.10)	0.86
Adult[c]	0.89 (0.59-1.33)	0.56
Residual	0.98 (0.42-2.32)	0.97
Smoking		
Childhood	1.93 (1.26-2.94)	0.002
Adult	1.56 (0.99-2.46)	0.05
Residual	1.78 (1.11-2.86)	0.02
Family history of coronary heart disease		
	2.28 (1.48-3.53)	<0.001

[a] Adjusted for sex and age. Residual indicates the independent association for childhood risk factor after additional adjustment for the equivalent adult risk factor.

[b] Due to low number of participants with high diastolic blood pressure and elevated triglycerides in childhood relative risks were not able to be estimated.

[c] $p<0.1$ for adult overweight by sex interaction.

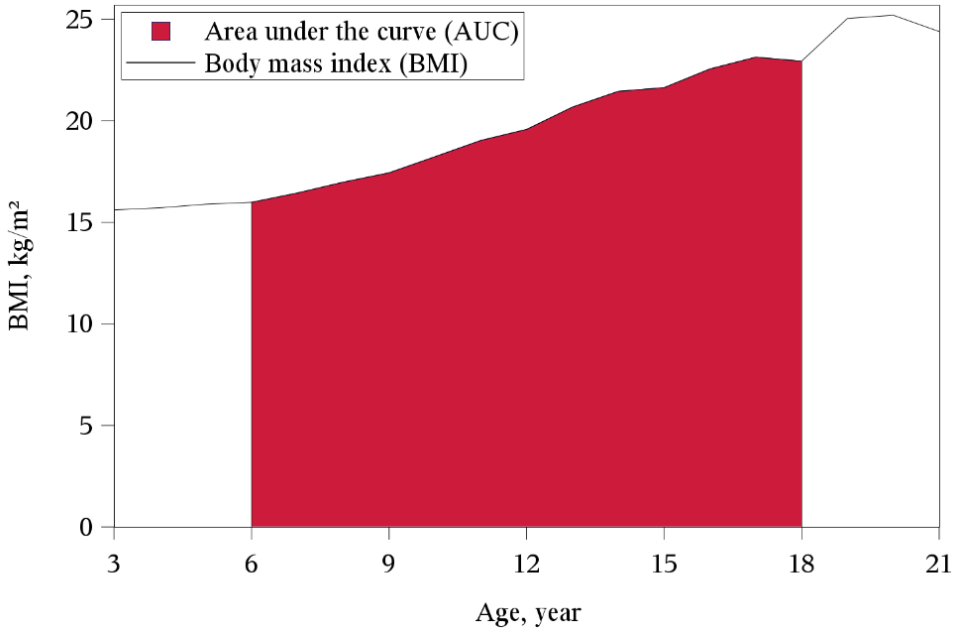
Table 3. Multivariable models showing relative risks (RR) and 95% confidence intervals (CI) between risk factors and carotid plaque

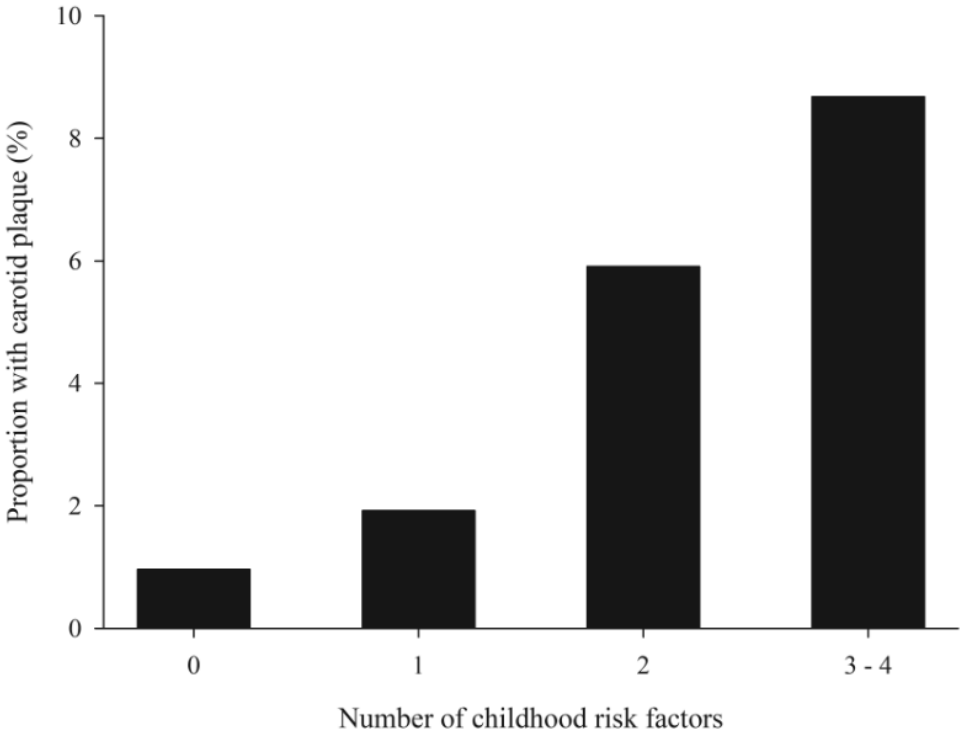
	RR (95% CI)	*p* value
Model 1[a]		
Childhood elevated systolic blood pressure	1.47 (0.94-2.29)	0.09
Childhood dyslipidemia	2.94 (1.71-5.05)	<0.001
Childhood overweight	0.76 (0.32-1.80)	0.54
Childhood smoking	2.04 (1.34-3.11)	<0.001
Family history of coronary heart disease	2.14 (1.38-3.31)	<0.001
Model 2[b]		
Adult elevated systolic blood pressure	1.16 (0.70-1.95)	0.56
Adult dyslipidemia	2.85 (1.49-5.43)	0.002
Adult overweight	0.75 (0.50-1.12)	0.16
Adult smoking	1.48 (0.94-2.33)	0.09
Family history of coronary heart disease	2.22 (1.43-3.44)	<0.001
Model 3[c]		
Childhood elevated systolic blood pressure	1.43 (0.92-2.22)	0.11
Childhood dyslipidemia	2.41 (1.36-4.24)	0.002
Childhood overweight	0.79 (0.31-2.00)	0.62
Childhood smoking	1.93 (1.21-3.09)	0.006
Family history of coronary heart disease	2.11 (1.36-3.27)	<0.001

[a] Model 1 with all childhood risk factors and family history of coronary heart disease. Adjusted for sex and age.

[b] Model 2 with all adult risk factors and family history of coronary heart disease. Adjusted for sex and age.

[c] Model 3 indicates the independent association for childhood risk factors when adjusted for sex, age, and all adult risk factors.


Area under the curve (AUC)
Body mass index (BMI)
BMI, kg/m²
25
20
15
10
5
0
3
6
9
12
15
18
21
Age, year


Proportion with carotid plaque (%)
10
8
6
4
2
0
0
1
2
3 - 4
Number of childhood risk factors

Supplemental material

Childhood risk factors and carotid atherosclerotic plaque in adulthood: The Cardiovascular Risk in Young Finns Study

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Supplemental Table 1. Flowchart for the Cardiovascular Risk in Young Finns Study

Study year	No.[a]	Age cohorts																			
1980	3596	3	6	9	12	15	18														
1983	2991		6	9	12	15	18	21													
1986	2799			9	12	15	18	21	24												
1989	2737[b]				12	15	18	21	24	27											
1992	2730[c]					15	18	21	24	27	30										
2001	2620[d]								24	27	30	33		36		39					
2007	2243[d]										30	33		36		39		42		45	
2011	2115												34		37		40		43		46	49

[a] No. refers to the number of subjects who participated in any phase of the study in a given year.

[b] In 1989, physical examinations and blood tests were gathered only in one center (N=632).

[c] In 1992, cohorts from Helsinki, Kuopio and Turku areas were included for blood sampling and/or physical examinations (N=891). In 1992, the limitation in sampling size was due to economic constraints.

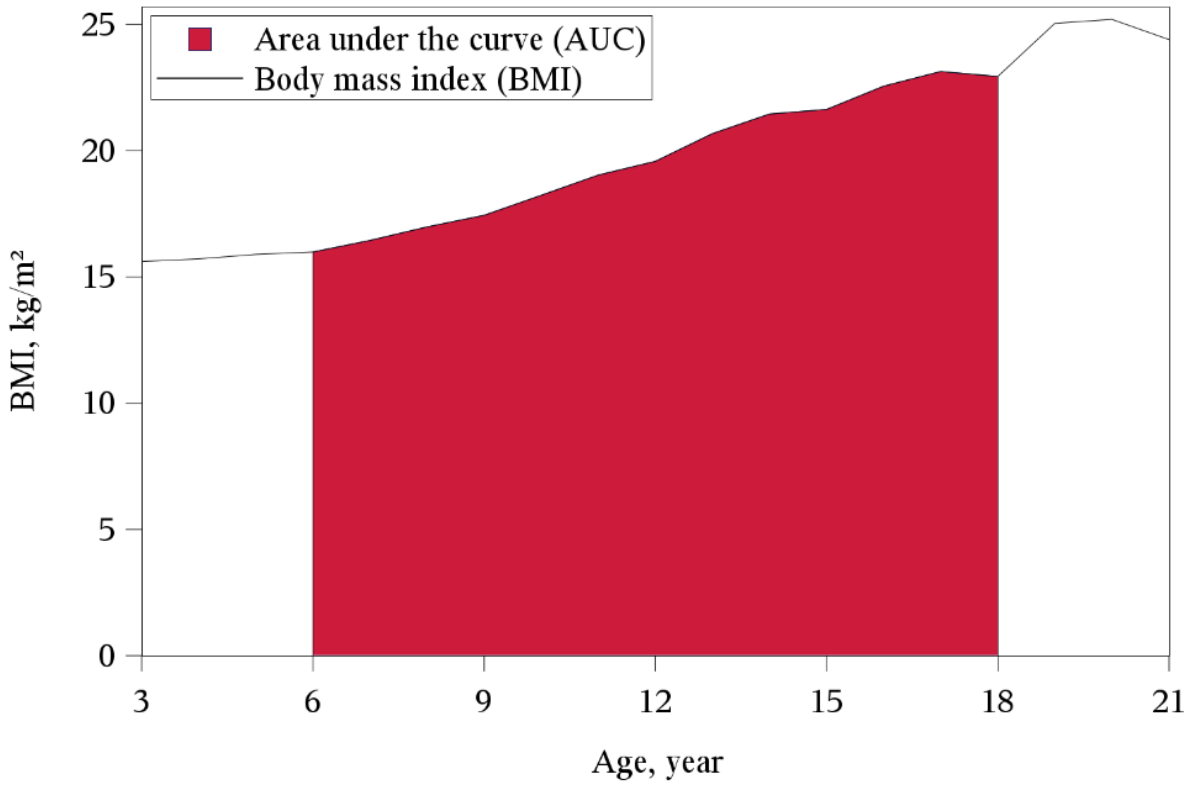
[d] In 2001 and 2007, carotid ultrasound was performed to 2283 and 2204 participants, respectively.

Supplemental Methods

Area under the curve – childhood risk factor long-term burden

Area under the curve (AUC) was defined for childhood blood pressure, BMI, and serum lipids as a measure of childhood risk factor long-term cumulative burden. AUC variables were generated using repeatedly measured data from 1980 to 2011 (measurements from 3-34 years and for diastolic blood pressure from 6-34 years). First, subject-specific curves were estimated by mixed model regression splines.[1] The covariance structure for the longitudinal setting was modelled by allowing for subject-specific regression spline coefficients, which were incorporated as random effects into the model. To avoid overfitting at participant level, the number of knots were reduced on the calendar time for the subject-specific part from that of the fixed effect parts on age. For triglycerides and diastolic blood pressure, the number of knots on age were reduced for the subject-specific part from that of the fixed effect parts on the calendar time. The mean profile was allowed to vary across birth cohorts, ages, gender and in case of blood pressure family's area of residence at the beginning of the study and in case of diastolic blood pressure parent's hypertension in terms of possibly different fixed effect parts. Then, similar to the approach of Lai et al,[2] AUCs were evaluated for each risk factor for the age period of 6-18 years as a measure of childhood risk factor long-term cumulative burden.

Supplemental Figure 1. Graphical illustration for the area under the curve



Supplemental Table 2. Relative risks (RR) and 95% confidence intervals (CI) between Z-scores and the presence of carotid plaque[a]

	RR (95%CI)	*p* value
Systolic blood pressure		
Childhood	1.21 (0.99-1.47)	0.06
Adult	1.09 (0.89-1.35)	0.40
Residual	1.21 (0.97-1.50)	0.09
Diastolic blood pressure		
Childhood	1.58 (1.25-2.00)	<0.001
Adult	0.98 (0.78-1.22)	0.83
Residual	1.70 (1.33-2.18)	<0.001
Lipids and lipoproteins		
Total cholesterol		
Childhood	1.56 (1.30-1.88)	<0.001
Adult	1.56 (1.31-1.84)	<0.001
Residual	1.27 (0.99-1.63)	0.06
LDL-cholesterol		
Childhood	1.76 (1.46-2.11)	<0.001
Adult	1.67 (1.41-1.98)	<0.001
Residual	1.42 (1.08-1.86)	0.01
HDL-cholesterol		
Childhood	0.88 (0.72-1.06)	0.17
Adult	0.80 (0.64-1.00)	0.05
Residual	0.97 (0.74-1.27)	0.84

Non-HDL-cholesterol		
Childhood	1.64 (1.37-1.96)	<0.001
Adult	1.61 (1.38-1.88)	<0.001
Residual	1.32 (1.03-1.69)	0.03
Triglycerides		
Childhood	0.98 (0.74-1.29)	0.88
Adult[b]	1.22 (1.00-1.48)	0.05
Residual	0.82 (0.59-1.14)	0.23
Body mass index		
Childhood	0.95 (0.78-1.17)	0.64
Adult[c]	0.82 (0.69-0.99)	0.04
Residual	1.13 (0.85-1.51)	0.40

[a] Relative risk indicates the change in risk for having carotid plaque in adulthood for a 1 SD increase in the risk factor level. Models are adjusted for sex and age. Residual indicates the independent association for childhood risk factor after additional adjustment for the equivalent adult risk factor.

[b] Due to skewness, adult triglycerides were log-transformed.

[c] $p<0.1$ for adult body mass index by sex interaction.

Supplemental Table 3. Childhood smoking volume and adulthood carotid plaque

	Proportion with carotid plaque	RR[a]	95% CI[b]	*p* value
Childhood smoking volume				
Never smoked	1.9 %	1.0	Referent	Referent
1 cigarette	2.3 %	1.14	0.42-3.09	0.80
2 to 50 cigarettes	4.0 %	1.86	0.99-3.50	0.06
Over 50 cigarettes	5.1 %	2.27	1.24-4.15	0.008
p for trend				0.005

[a] Relative risk (RR) indicates the change in risk for having carotid plaque in adulthood when compared with the referent group (never smoked). Adjusted for sex and age.

[b] CI indicates the confidence intervals.

Supplemental Table 4. Multivariable models showing relative risks (RR) and 95% confidence intervals (CI) between Z-scores, smoking, family history of coronary heart disease and the presence of carotid plaque

	RR (95% CI)[a]	*p* value
Model 1[b]		
Childhood systolic blood pressure	1.21 (0.98-1.50)	0.08
Childhood LDL cholesterol	1.70 (1.42-2.04)	<0.001
Childhood body mass index	0.86 (0.69-1.07)	0.17
Childhood smoking	2.01 (1.32-3.06)	0.001
Family history of coronary heart disease	2.05 (1.32-3.17)	0.001
Model 2[c]		
Adult systolic blood pressure	1.08 (0.87-1.33)	0.51
Adult LDL cholesterol	1.66 (1.40-1.96)	<0.001
Adult body mass index	0.73 (0.59-0.91)	0.004
Adult smoking	1.38 (0.88-2.18)	0.16
Family history of coronary heart disease	2.18 (1.39-3.41)	<0.001
Model 3[d]		
Childhood systolic blood pressure	1.22 (0.95-1.55)	0.12
Childhood LDL cholesterol	1.33 (0.99-1.78)	0.06
Childhood body mass index	1.12 (0.82-1.53)	0.48
Childhood smoking	1.98 (1.23-3.18)	0.005
Family history of coronary heart disease	2.07 (1.32-3.24)	0.002

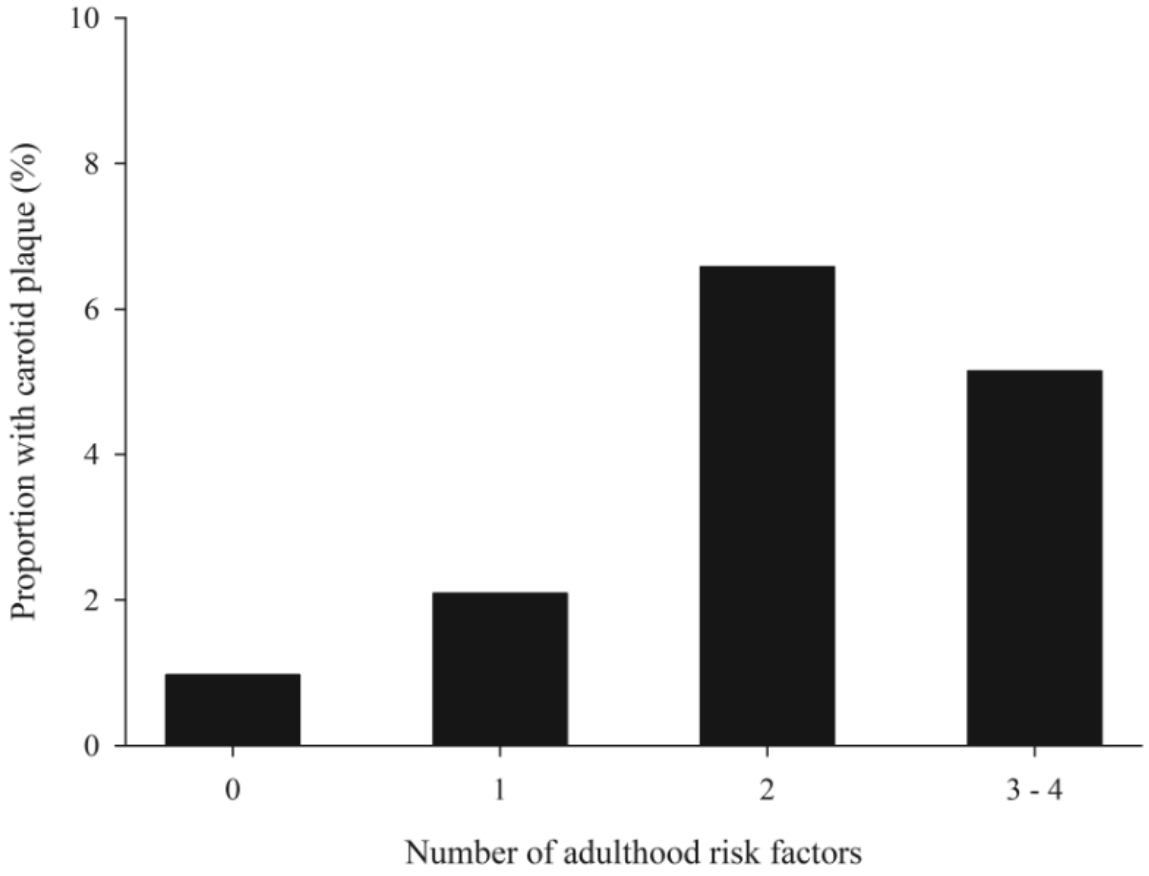
[a] Relative risk indicates change in risk for having carotid plaque for a 1 SD increase in risk factor level.

[b] Model 1 with all childhood risk factors and family history of coronary heart disease. Adjusted for sex and age. N=2565 in no plaque group and n=88 in plaque group.

[c] Model 2 with all adult risk factors and family history of coronary heart disease. Adjusted for sex and age. N=2462 in no plaque group and n=86 in plaque group.

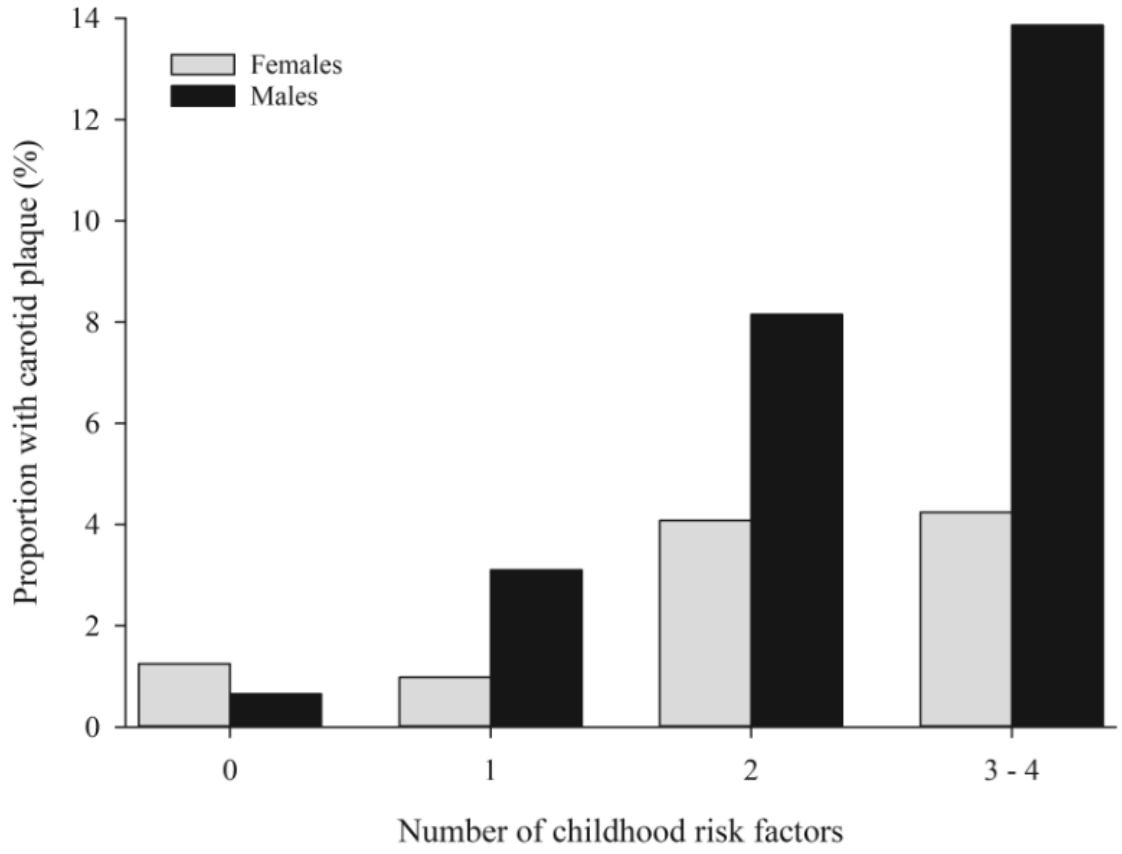
[d] Model 3 indicates the independent association for childhood risk factors when adjusted for sex, age, and all adult risk factors. N=2462 in no plaque group and n=86 in plaque group.

Supplemental Figure 2. Proportion of participants with carotid plaque according to the number of adult risk factors



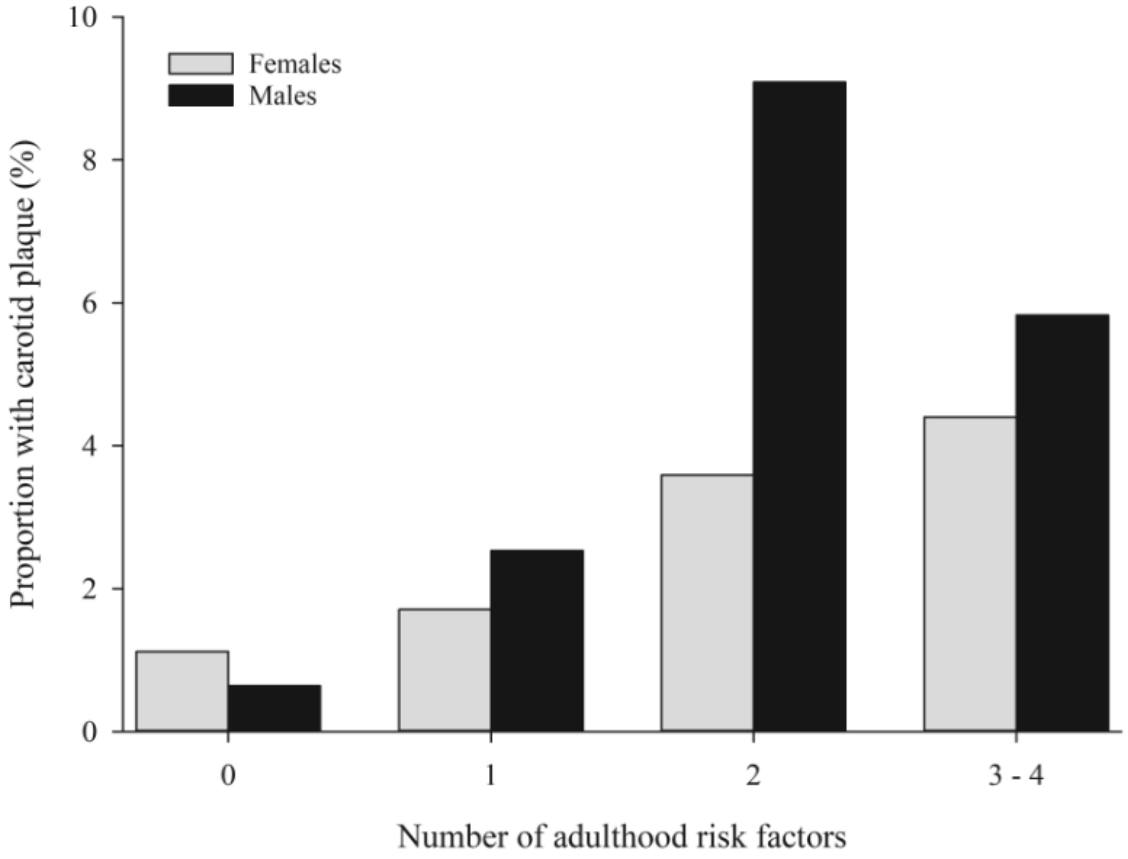
One point was given for each risk factor classified as abnormal. Risk factors included were dyslipidemia, elevated systolic blood pressure, smoking, and family history of coronary heart disease. Carotid plaque (%) indicates the proportion of participants with carotid plaque across different groups. N for 0, 1, 2 and 3 to 4 risk factor groups are 513, 1198, 730, and 194, respectively.

Supplemental Figure 3. Proportion of participants with carotid plaque according to the number of childhood risk factors, stratified by sex



One point was given for each risk factor classified as abnormal. Risk factors included were dyslipidemia, elevated systolic blood pressure, smoking, and family history of coronary heart disease. Carotid plaque (%) indicates the proportion of participants with carotid plaque across different groups. N for females in 0, 1, 2, and 3 to 4 risk factor groups are 320, 610, 392, and 118, and for males 307, 484, 319, and 101, respectively.

Supplemental Figure 4. Proportion of participants with carotid plaque according to the number of adult risk factors, stratified by sex



One point was given for each risk factor classified as abnormal. Risk factors included were dyslipidemia, elevated systolic blood pressure, smoking, and family history of coronary heart disease. Carotid plaque (%) indicates the proportion of participants with carotid plaque across different groups. N for females in 0, 1, 2, and 3 to 4 risk factor groups are 357, 645, 334, and 91, and for males 156, 553, 396, and 103, respectively.

Supplemental References

1. Welham SJ. Smoothing spline models for longitudinal data. In: Fitzmaurice G, Davidian M, Verbeke G, Molenberghs G, eds. Longitudinal data analysis. Handbooks of modern statistical methods. 1st ed. Boca Raton, Florida: *Chapman & Hall/CRC,* 2009:253-289.

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